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PATENT#8
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10-1001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of:

PODBIELSKI

Serial No.: 09/494,297

Filed: January 31, 2000

For: COLLAGEN-BINDING PROTEINS FROM
STREPTOCOCCUS PYOGENES

Examiner: N. Minnifield

Art Unit: 1645

Docket No.: P06628US0/BAS

DECLARATION UNDER 37 C.F.R. § 1.131Assistant Commissioner for Patents
Washington, DC 20231


S I R:

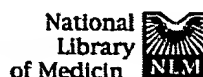
I, Andreas Podbielski, declare and state as follows:

1. I am the sole inventor of the above-identified patent application. I am also the principle author of the journal article, *Characterization of nra, a global negative regulator gene in group A streptococci*, published in *Molecular Microbiology* (1999) 31(4), pages 1051-1064 (hereinafter the "Article").
2. The claimed subject matter which is disclosed in the Article is exclusively my own and therefore not the product of another.
3. Co-authors of the Article, Markus Woischnik, Bettina A.B. Leonard and Karl-Hermann Schmidt worked at my direction and assisted me in preparing and writing the Article but did not contribute to the subject matter of the claimed invention.
4. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements

and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: Sept. 18, 2001


Prof. Dr. Dr. A. Podbielski
Arzt für Med. Mikrobiologie
und Infektionsepidemiologie
Andreas Podbielski



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☐ 1: Mol Microbiol 1999 Feb;31(4):1051-1064

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Characterization of nra, a global negative regulator gene in group streptococci.

Podbielski A, Woischnik M, Leonard BA, Schmidt KH.

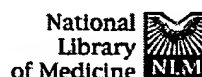
Department of Medical Microbiology and Hygiene, University Hospital Ulm, Germany. andreas.podbielski@medizin.uni-ulm.de

During sequencing of an 11.5 kb genomic region of a serotype M49 group A streptococcal (GAS) strain, a series of genes were identified including nra(negative regulator of GAS). Transcriptional analysis of the region revealed that nra was primarily monocistronically transcribed. Polycistronic expression was found for the three open reading frames (ORFs) downstream and for the four ORFs upstream of The deduced Nra protein sequence exhibited 62% homology to the GAS RofA positive regulator. In contrast to RofA, Nra was found to be a negative regulator of own expression and that of the two adjacent operons by analysis of insertional inactivation mutants. By polymerase chain reaction and hybridization assays of 10 different GAS serotypes, the genomic presence of nra, rofA or both was demonstrated. Nra-regulated genes include the fibronectin-binding protein F2 gene (prtF2) and a novel collagen-binding protein (cpa). The Cpa polypeptide was purified as a recombinant maltose-binding protein fusion and shown to bind type I collagen but fibronectin. In accordance with nra acting as a negative regulator of prtF2 and cpa, levels of attachment of the nra mutant strain to immobilized collagen and fibronectin was increased above wild-type levels. In addition, nra was also found to regulate negatively (four- to 16-fold) the global positive regulator gene, mga. Using a strain carrying a chromosomally integrated duplication of the nra 3' end and an nra-luciferase reporter gene transcriptional fusion, nra expression was observed to reach its maximum during late logarithmic growth phase, while no significant influence of atmospheric conditions could be distinguished clearly.

PMID: 10096074 [PubMed - indexed for MEDLINE]

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Related Articles, Books, Lin

M protein and protein F act as important determinants of cell-specific tropism of Streptococcus pyogenes in skin tissue.**Okada N, Pentland AP, Falk P, Caparon MG.**

Department of Molecular Microbiology, Washington University School of Medicine, St. Louis, Missouri 63110-1093.

The pathogenic gram-positive bacterium *Streptococcus pyogenes* (group A streptococcus) causes numerous diseases of cutaneous tissue, each of which is initiated after the interaction of the bacterium with the cells of the epidermis. In this study, we show that different surface proteins of *S. pyogenes* play important roles in determining the cell-specific tropism of the bacterium in skin. Using streptococcal strains with defined mutations in the genes which encode surface proteins in combination with primary cultures of human skin and an in situ adherence assay which uses histological sections of human skin, we show that the M protein of *pyogenes* mediates the binding of the bacterium to keratinocytes, while a second streptococcal surface protein, protein F, directs the adherence of the organism to Langerhans' cells. Characterization of binding revealed that adherence was inhibited by purified streptococcal proteins and pretreatment of both host cells with the protease trypsin. Adherence was only slightly affected by the state of keratinocyte differentiation in vitro, but was considerably modulated in response to environmental conditions known to regulate expression of M protein and protein F, suggesting that the interaction between these bacterial cell-surface structures/adhesins and keratinocytes and Langerhans' cells may play an important role in streptococcal skin disease.

PMID: 8083381 [PubMed - indexed for MEDLINE]

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